Shaded amino acids were incorporated erroneously in the following locations.

Location	Sequence
Specification (Page 3, line 22)	VKEK/QKKXXGKGPGGXPPPK
Claim 1 (Page 38, line 4)	VKEK/QKKXXGKGPGGXPPK
Sequence listing SEQ ID NO:1	VKEK/QKKXXGKGPGGXPPPK

The correct length of SEQ ID NO: 1 should be 17 amino acids. A sequence listing with the correct SEQ ID NO: 1 sequence is submitted concurrently with this amendment. Applicants request incorporation of the corrected SEQ ID NO: 1. Comparison of amino acid sequences of human, pig, and mouse AMP-18 as in positions 103-119 in FIG. 10 (see table below) indicates that the extra amino acids in SEQ ID NO: 1 were inserted erroneously.

Species	AMP-18 amino acid positions 103-119 in FIG. 10
Human	VKEKKLQGKGPGGPPPK
Pig	VKEKKLQGKGPGGPPPK
Mouse	VKEQK . . GKGPGGAPPK

Correction of this obvious error in SEQ ID NO: 1 will moot the written description rejection to claims raised by the examiner.

IV. The Specification Does Contain an Enabling Disclosure

Claims 1, 5, 6, 11, 13-15, 22 and 27-29 were rejected by the examiner under 35 U.S.C. 112, first paragraph for lack of an enabling disclosure in the specification. However, as the following arguments demonstrate, the specification contains enabling disclosure for claims 1, 5, 6, 11, 13-15, 22 and 27-29.

A. No Undue Experimentation is Required to Practice the Invention

On page 6 of the Action, the examiner stated that the claimed invention places an undue burden because a skilled artisan would have to engage in empirical experimentation to identify proteins produced by gastric epithelium. The applicants disagree that the invention places an undue burden on a skilled artisan. The Court of Appeals for the Federal Circuit in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) states that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance

> with respect to the direction in which the experimentation should proceed.

To practice the present invention, only routine experimentation is required and a reasonable amount of guidance is present in the specification. The applicants analyzed AMP-18 amino acid sequences from human, pig, and mouse to arrive at the sequences claimed. In addition, the bioactivity of various peptides derived from AMP-18 proteins provide support for the claimed sequence (see Table 1 in the specification). The specification provides guidance to select peptides that are more likely to have positive or negative effects (see page 29, lines 12-20, 25-30 in the specification). Those of skill in the art would know to substitute similar amino acids in synthetic peptides and perform the routine assays to see if the criteria of the inventions are met. The bioactivity assays involve simple monitoring of cell growth for 4 days stimulated by desired peptides or protein extract (see page 11, lines 4-15 in the specification). The bioactivity profiles of 12 peptides are outlined in Table 1 of the specification. Based on that analysis, a well defined 14-amino acid mitogenic domain in AMP-18 has been identified. Bioactivity studies and sequence alignments have provided the basis for the variation claimed. Therefore, practice of the invention as claimed does not place an undue burden on a skilled artisan.

B. Reasonable Correlation Between the Disclosed *in vitro* Utility and an *in vivo* Activity is Sufficient for an Enabling Disclosure

On page 8 of the Action, the examiner stated that:

> There is, however, no evidence provided that administering the described AMP-18 peptides or proteins has any effect on healing ulcers *in vivo*. In fact, there is no evidence provided to indicate that intestinal epithelial cells in the region of an ulcer, *in vivo*, express a AMP-18 receptor.

The applicants established the growth stimulating activities of AMP-18-derived peptides in gastric epithelial cells (page 20, Table 1; FIG. 11). It is well known in the art that *in vitro* cell culture studies convey a reasonable prediction for *in vivo* activities. A rigorous or an invariable correlation is not required, as stated in *Cross v. Iuzuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

In addition, the applicants emphasize that according to MPEP 2164. 05:

> ...considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].").

In page 13, lines 10-20 of the specification, the applicants disclose that AMP-18 structural domains resemble the anti-microbial magainins and thus AMP-18 may interfere with *Helicobacter pylori*, a causative agent for many duodenal ulcers. Therefore, the applicants have established substantial experimental evidence *in vitro* that AMP-18-derived peptides stimulate epithelial growth and these results can be reasonably correlated to have therapeutic utility *in vivo*. The inventors attestations must be accepted as credible.

C. Disclosure of AMP-18 Receptor Expression is Not Relevant to Practice the Present Invention

On page 9 of the Action, the examiner stated:

> ...the disclosure does not provide guidance as to when or where the AMP-18 receptor is expressed in vivo and thus the skilled artisan would have to engage in empirical experimentation to identify cells in the gastrointestinal tract of mammals that respond to AMP-18 in order to practice the method.

The specificity of AMP-18 activity *in vivo* may be due to the specificity of AMP-18 expression rather than the localization of AMP-18 receptor (page 32, lines 8-10 of the specification). In addition, the localization of AMP-18 protein in the antrum mucosal tissue was disclosed in the specification (page 18, lines 5-12). The AMP-18 protein was concentrated in mucosal epithelial cells lining the stomach lumen. The localization of a putative AMP-18 receptor is not necessary to practice the invention because the knowledge of AMP-18 expression will guide a skilled artisan to design appropriate treatment methods.

V. <u>On Pages 10-11 of the Action the Examiner Questions Claim Terms</u>

(i) The examiner rejected claims 1, 2, 5, 6, 13-15, 22, and 27-29 as being indefinite for failing to disclose the metes and bounds of the term "homologous".

> If an applicant does not define a term in the specification, that term will be given its "common meaning." *Paulsen*, at 30 F. 3d 1480, 31 USPQ2d at 1674.

Standard definition of "homology" or "sequence homology" is:

> The extent of identity between two nucleotide or amino acid sequences, as a measure for a common evolutionary origin. *The Dictionary of Gene Technology*, 2nd Edition, WILEY-VCH, 2001.

The claims refer to peptides related through common evolution. The adjacent homology could be detected.

(ii) The examiner rejected claim 11 because claim 11 refers to a peptide of indeterminate length. Claim 11 is amended to reflect the amino acid sequence specified by SEQ ID NO: 2.

(iii) Amended claims 2-4 are independent and therefore moot the examiner's rejection for lack of antecedent basis.

(iv) Amended claim 2 reflects the processed form of pig AMP-18 amino acid sequence as in positions 21 to 185 in FIG. 8.

(v) On page 11 of the Action, the examiner stated:

> Claim 3 is also indefinite because it is drawn to an isolated protein comprising the sequence set forth in Figure 8...

To the contrary, claim 3 is drawn to an isolated protein comprising an amino acid sequence set forth in FIG. 3.

(vi) The examiner rejected claims 7-11 as indefinite for failing to set forth the definition of "synthetic". In page 17, lines 3-6 of the specification, the term "synthetic" refers to peptides that were chemically synthesized.

VI. Hayashizaki *et al.* (8 Febraury 2001) Does Not Anticipate Claims 4 and 11

The examiner rejected claims 4 and 11 over Hayashizaki *et al.* (8 February, 2001).

Claim 4 is amended to reflect the processed form of mouse AMP-18 protein that lacks the signal peptide. Hayashizaki *et al.* does not disclose the claimed protein.

Claim 11 refers to SEQ ID NOS: 2 and 3. SEQ ID NO: 2 (23 amino acids) is not identified in Hayashizaki (184 amino acids). SEQ ID NO: 3 relates to a peptide sequence derived from human AMP-18 sequence, whereas Hayashizaki *et al.* discloses only deduced peptides from mouse cDNA sequences of different length. Therefore, Hayashizaki *et al.* does not anticipate claims 4 and 11.

VII. Claims 2-3 and 11 are Not Anticipated by Jacobs *et al.* (1999, WO 99/07840).

Claim 2 refers to an AMP-18 amino acid sequence from pig (SEQ ID NO: 18). However, Jacobs *et al.* discloses a cDNA sequence and a predicted amino acid sequence from human. Comparing SEQ ID NO: 18 to an amino acid sequence from human in Jacobs *et al.* reveals specific differences. For example, amino acids at positions 6, 16, and 21 of SEQ ID NO: 18 are Ala, Thr, and Asp respectively. In Jacobs *et al*, the corresponding amino acids are Val, Ala, and Asn. In addition, the amino acid sequence in Jacobs *et al.*, to which the examiner refers, consists of 185 amino acids, whereas claim 2 refers to a protein with only 165 amino acids. Jacobs *et al.* does not teach the protein in claim 2. Therefore Jacobs *et al.* does not anticipate claim 2.

The SEQ ID NO: 2 in claim 11 relates to a peptide derived from mouse AMP-18 protein. Comparison of the sequence disclosed in SEQ ID NO: 2 of the present application with that of Jacobs *et al.* reveals several differences. For example, in SEQ ID NO: 2, amino acids at positions 3 and 4 are Thr and Met respectively. The corresponding amino acids in Jacobs *et al.* are Ala and Leu. Furthermore, SEQ ID NO: 2 has 23 amino acids, where as the sequence in Jacobs *et al.* has 185 amino acids. SEQ ID NO: 3 in claim 11 has 14 amino acids. No such peptide is identified in Jacobs *et al.* Jacobs *et al.* does not anticipate claims 2 and 11, because the sequences mentioned in claims 2 and 11 are different than the one taught by Jacobs *et al.*

Claim 3 refers to SEQ ID NO: 13. Comparison of SEQ ID NO: 13 with Jacobs *et al.* (Jacobs SEQ ID NO: 18) reveals that at amino acid position 87, the present application has Lys whereas Jacobs *et al.* has Asn. Therefore, claim 3 is not anticipated by Jacobs *et al.* Furthermore, the cDNA clone in Jacobs *et al.*, to which the examiner refers, relates to a cDNA molecule isolated from an adult human placenta cDNA library. There was no experimental evidence in Jacobs *et al.* to assign a biological function to the amino acid sequence predicted from the cDNA clone and there was no evidence that the protein belonged to gastrokines.

To anticipate a claim, the reference must teach every element of the claim.

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).
>
> The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Therefore, claims 2-3, and 11 are not anticipated by Jacobs *et al.*

VIII. Claims 2-3 and 11 Are Not Anticipated by Powell (1987).

Amended claim 2 relates to a processed form of pig AMP-18 protein having 165 amino acids that lacks the signal peptide. The amino acid sequence taught by Powell has 185 amino acids. Powell neither discloses the processed form of pig AMP-18 protein nor predicts the boundaries of the processed polypeptide. Therefore, Powell does not anticipate claim 2.

Claim 3 relates to a human amino acid sequence designated SEQ ID NO: 13. Comparison of SEQ ID NO: 13 with that of Powell reveals specific differences. In Powell, amino acid number 25 in FIG. 18 is Asn. However, the amino acid at corresponding position in SEQ ID NO: 13 is Asp. In addition, amino acid number 58 in Powell (FIG. 18) is Asn, and Asp in SEQ ID NO: 13. Therefore, Powell does not anticipate claim 3.

In claim 11, SEQ ID NOS: 2 and 3 appear. SEQ ID NO: 2 relates to a mouse AMP-18 derived peptide sequence of 23 amino acids. No such peptide is identified in Powell. Powell does not disclose any amino acid sequence of AMP-18 from mouse. Furthermore, SEQ ID NO: 3 has 14 amino acids and no such peptide is disclosed in Powell. Therefore, Powell does not anticipate claim 11.

IX. Summary and Conclusion

For the reasons stated above, applicant requests allowance of all pending claims.

Please contact the applicants' representative if you have any questions.

No other fees are believed due at this time, however, please charge any additional deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21459/90913).

Respectfully submitted,

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February 5, 2003

MARKED-UP VERSION
PENDING CLAIMS
SERIAL NO. 09/821,726
ATTY DOCKET NO: 21459/90913

WE CLAIM:

1. (Amended) A group of isolated homologous cellular growth stimulating proteins designated gastrokines, said proteins produced by gastric epithelial cells and comprising the [amino acid] amino acids in the sequence VKEK/QK[K]XXGKGPGGXPPK (SEQ ID NO: 1).

2. (Amended) An isolated protein [from the group of claim 1, said protein] having a sequence of amino acids from positions 21 to 185 of the sequence as shown in [further characterized as comprising an amino acid sequence as in FIG. 7] FIG. 8 (SEQ ID NO: 18), said protein present in pig gastric epithelia in a processed form lacking the 20 amino acids which constitute a signal peptide sequence, having 165 amino acids and an estimated molecular weight of approximately 18 kD as measured by polyacrylamide gel [electophoresis] electrophoresis, said protein capable of being secreted.

3. (Amended) [A] An isolated protein [from the group of claim 1, further characterized as] comprising [an amino acid] amino acids in the sequence as in FIG. 3 (SEQ ID NO: 13) [, said sequence deduced from a human cDNA].

4. (Amended) [A] An isolated protein [from the group of claim 1, further characterized as] comprising [an amino acid] amino acids in the sequence as in FIG. 6 (SEQ ID NO: 16) [, said sequence predicted from mouse RNA and DNA].

5. A growth stimulating peptide derived from a protein of claim 1.

6. A modified peptide produced by the method comprising the following steps:

(a) eliminating major protease sites in an unmodified peptide amino acid sequence by amino acid substitution or deletion in the unmodified peptide derived from a protein of claim 1; and

(b) optionally introducing amino acid analogs of amino acids in the unmodified peptide.

7. (Amended) A synthetic growth stimulating peptide, having a sequence of amino acids [from] as in positions 78 to 119 [as] of the sequence shown in FIG. 3 (SEQ ID NO: 13).

8. (Amended) [The] A synthetic growth stimulating peptide [of claim 7, said peptide] having a sequence of amino acids from position 97 to position 117 as shown in FIG. 3 (SEQ ID NO: 13)

9. (Amended) [The] A synthetic growth stimulating peptide [of claim 7, said peptide] having a sequence of amino acids from position 97 to position 121 as shown in FIG. 3 (SEQ ID NO: 13).

10. (Amended) [The] A synthetic growth stimulating peptide [of claim 7, said peptide] having a sequence of amino acids from position 104 to position 117 as shown in FIG. 3 (SEQ ID NO: 13).

11. (Amended) An isolated bioactive peptide [comprising] consisting of a sequence selected from the group consisting of LDTMVKEQK[..]GKGPGGAPPKDLMY (SEQ ID NO: 2) and KKLQGKGPGGPPPK (SEQ ID NO: 3).

13. A composition used for the treatment of ulcers, said composition including at least a growth stimulating peptide of claim 5.

14. A pharmaceutical composition for the treatment of diseases associated with overgrowth of gastric epithelia, said compositions comprising an inhibitor of a protein of the group of claim 1 or of a growth stimulating peptide of claim 5.

15. A pharmaceutical composition for the treatment of diseases of the colon and small intestine, said diseases selected from the group consisting of ulcerative colitis and Crohn's Disease, said composition comprising at least a growth stimulating peptide of claim 5.

22. A method to stimulate growth of epithelial cells in the gastrointestinal tract of mammals, said method comprising :

(a) contacting the epithelial cells with a composition comprising a protein from the group of claim 1 or a peptide derived from a protein of claim 1, and

(b) providing environmental conditions for stimulating growth of the epithelial cells.

27. A method to stimulate migration of epithelial cells after injury to the gastrointestinal tract of mammals, said method comprising:

(a) contacting the epithelial cells with a composition comprising a protein from the group of claim 1 or a peptide derived from a problem of claim 1; and

(b) providing environmental conditions allowing migration of the epithelial cells.

28. A method for cytoprotection of damaged epithelial cells in the gastrointestinal tract of mammals, said method comprising:

(a) contacting the damaged epithelial cells with a composition comprising a protein of the group of claim 1 or a peptide derived from a protein of claim 1; and

(b) providing environmental conditions allowing repair of the epithelial cells.

29. The method of claim 28, wherein the damaged cells are an ulcer.